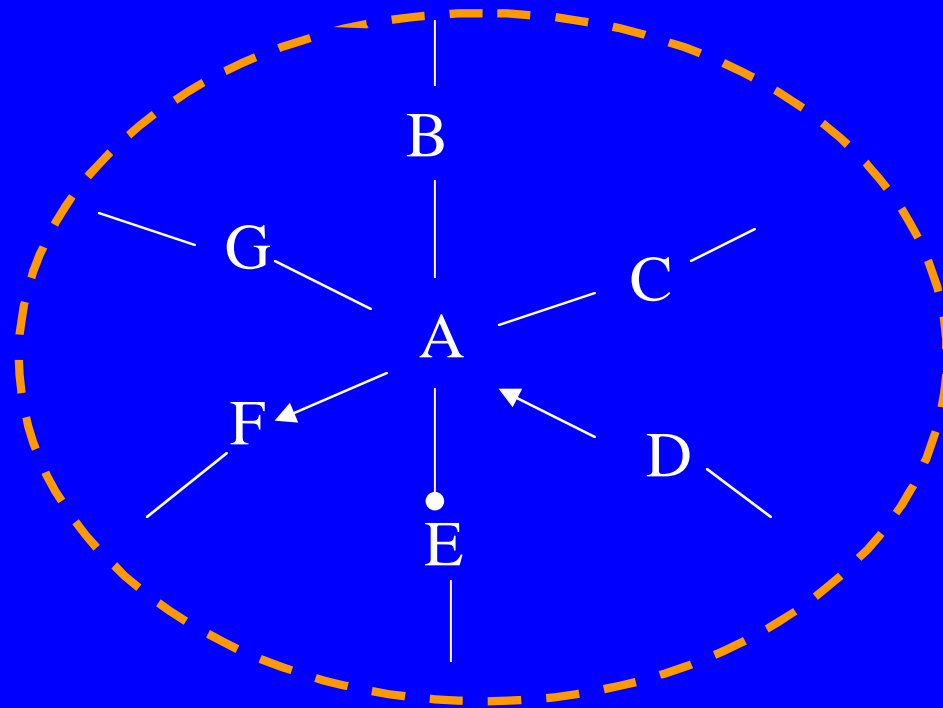# Understanding Protein Interactions

UCLA-DOE Laboratory of Structural Biology and Molecular Medicine

Principal Investigator: David Eisenberg

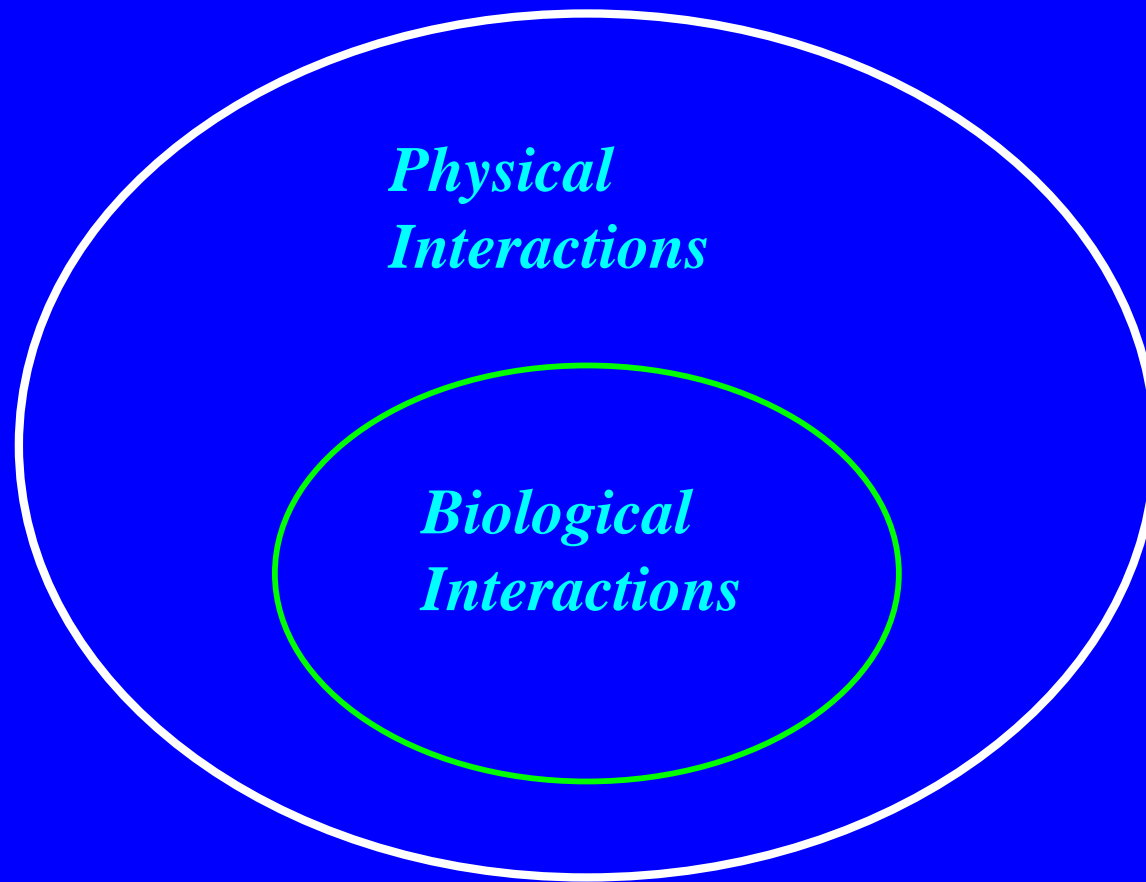Presenter: X. Joyce Duan

# Protein Interaction Networks inside Cells

Outline

- Compile protein interaction database
- Assess the reliability of protein interactions
- Analyze protein interaction networks

Physical Interactions vs. *Biological Interactions*
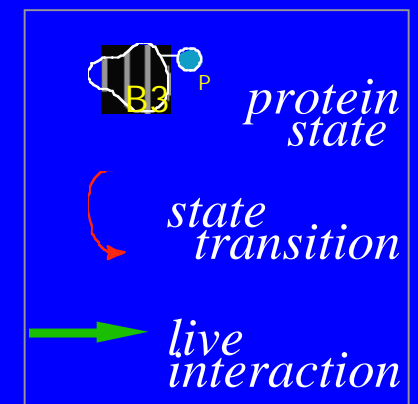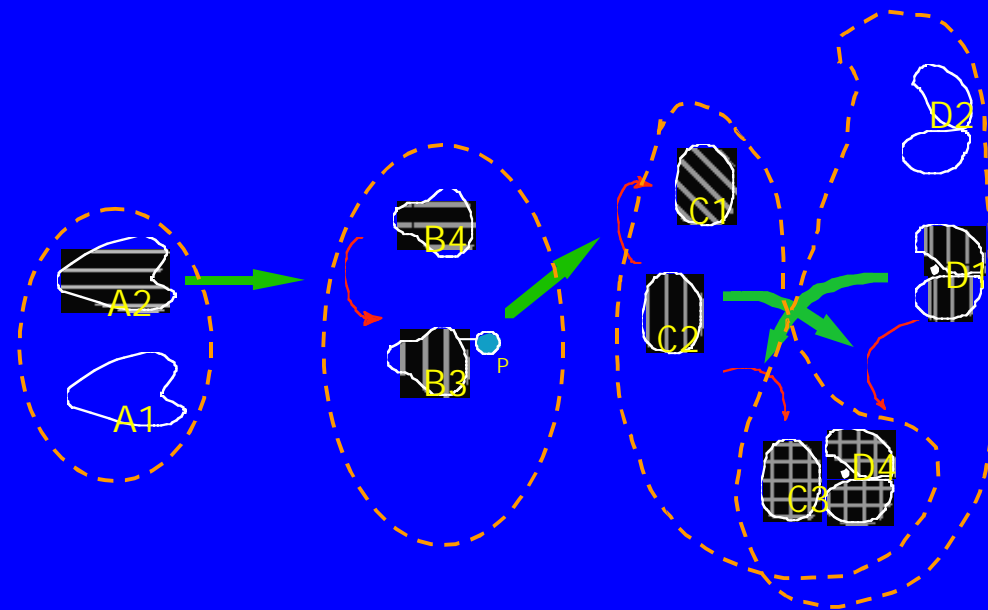
Physical Interactions

Biological Interactions

Layered Information about Protein Interactions

Physical Interactions

Biological Interactions
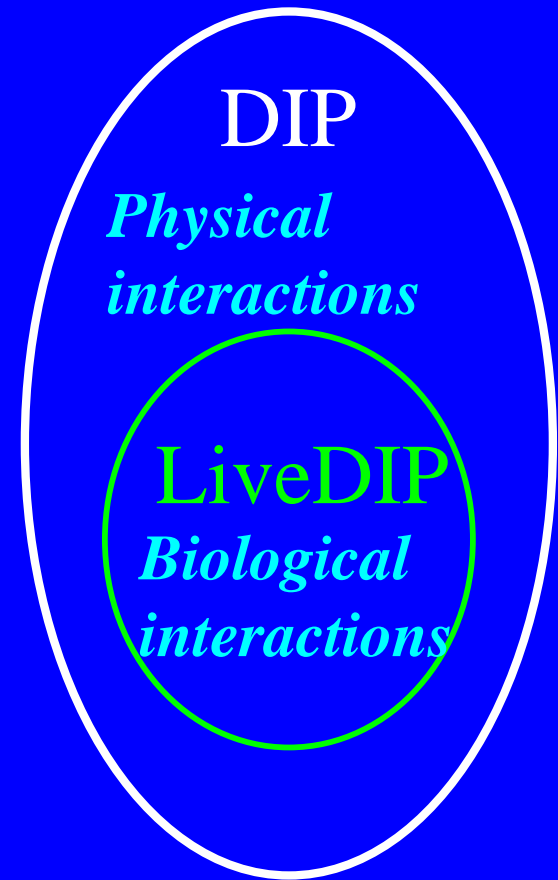
protein
interaction

protein state
state transition
live interaction
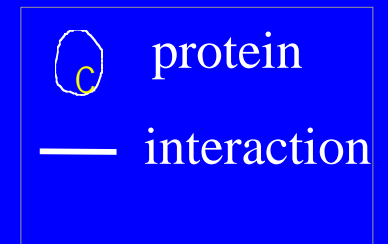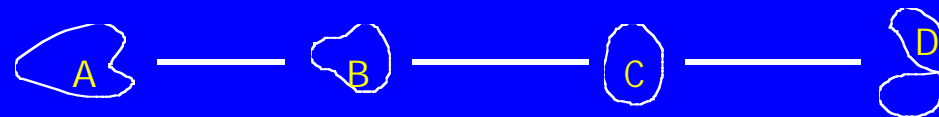
Database of Protein Interactions

DIP   interacting domains, binding affinity, experimental methods

LiveDIP   protein states, state transition

DIP
Physical interactions

LiveDIP
Biological interactions

http://dip.doe-mbi.ucla.edu

DIP 1175E						
Protein A	**DIP** DIP:310N		**PIR** ATBY	**SwissProt** ACT_YEAST	**GenBank** gi:71632	
	Name/Description actin					
Protein B	**DIP** DIP:973N		**PIR** S63211	**SwissProt** SLA2_YEAST		
	Name/Description cytoskeleton assembly control protein SL					
Experiments	**#**	**Method**				
	1	Sucrose gradient sedimentation			PMI	
	2	In vitro binding			PMI	

Protein State Page

Protein State	
State Key	981
Protein Name	FUS3
Modification	phosphorylation
Residue modified	T180,Y182
State by	STE7
Activity	active
Reference	8384702

Related Structure 1	
Alignment	Residues 6 to 350 out of total 353 residues align with 23 to 355 out of 365 residues of structure 2erk with 50 % identity.
PDB Code	2ERK
Structure Description	The activation loop is refolded bringing the phosphorylated Thr and Tyr into alignment with Arg−rich binding site surfaces. Conformational changes occur in the lip and neighboring structures, including the P+1 site. Domain rotation and remodeling of the Pro−directed P+1 specificity pocket account for the activation. Conformational changes outside the lip provide loci at which the state of phosphorylation ca be sensed by other cellular components.
Reference	9298898

Live Interaction Page

STE7 phosphorylates and activates FUS3.

979 STE7 →+P activation→ 981 FUS3 (P)

Description:
STE7 phosphorylates FUS3 at T180,Y182 and activates FUS3.

Annotations on the interaction:

LIVE_INTER_KEY	417
PMID	8384702
LIVE_COMMENT	Ste7 is the physiological activator of Fus3 involved in pheromone response. Signal transduction pathways in many, if not all, eukaryotic organisms use homologous kinase cascades.
IKEY	1027

Interaction requires:

Protein	STE7	Protein	FUS3
Activity	active	Activity	inactive
Protein state	979	Protein state	980

Compile protein interaction database

Data Acquisition

Score Medline abstracts

↓

Manual information extraction

↓

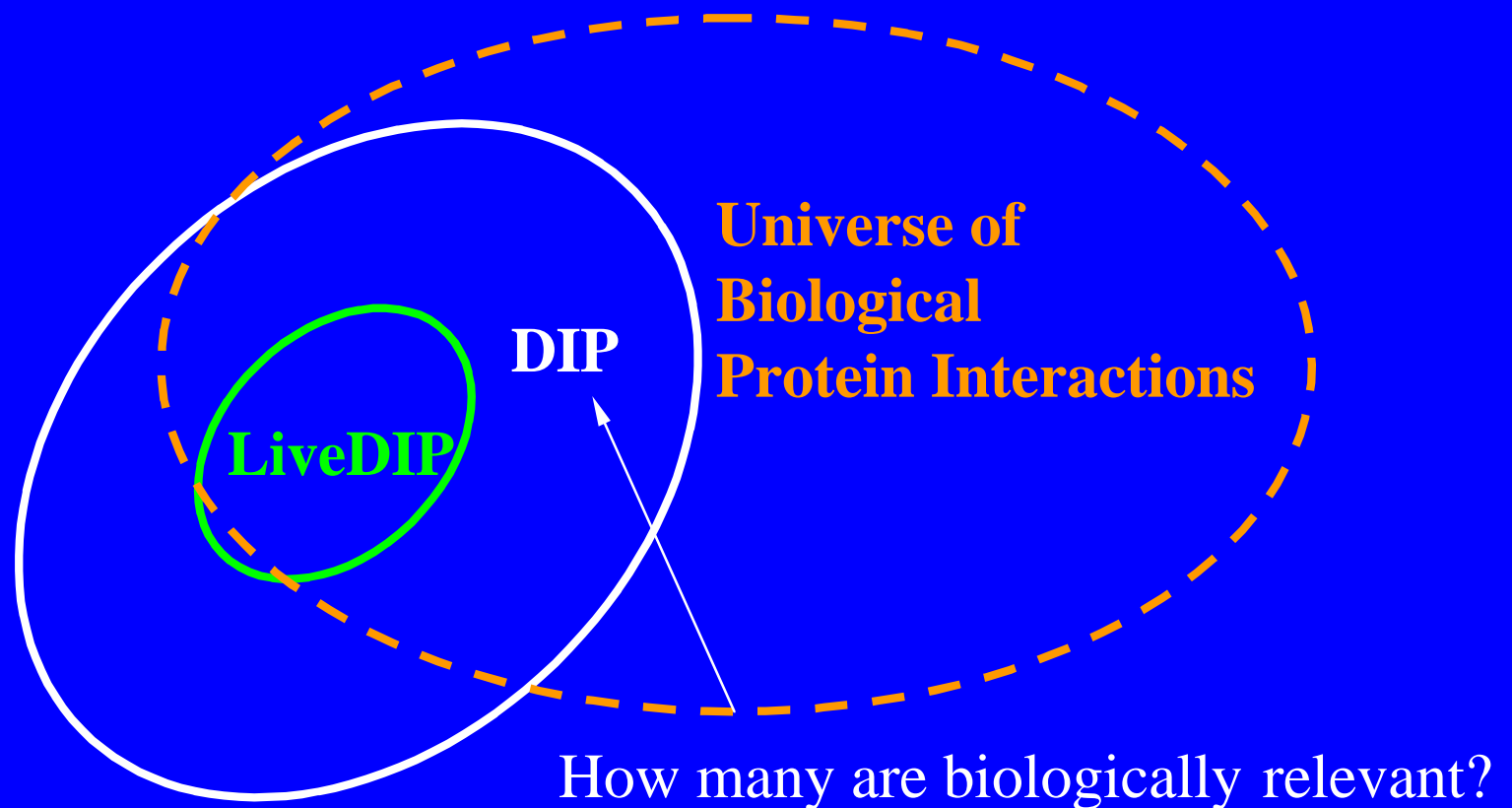Data entered through HTML form
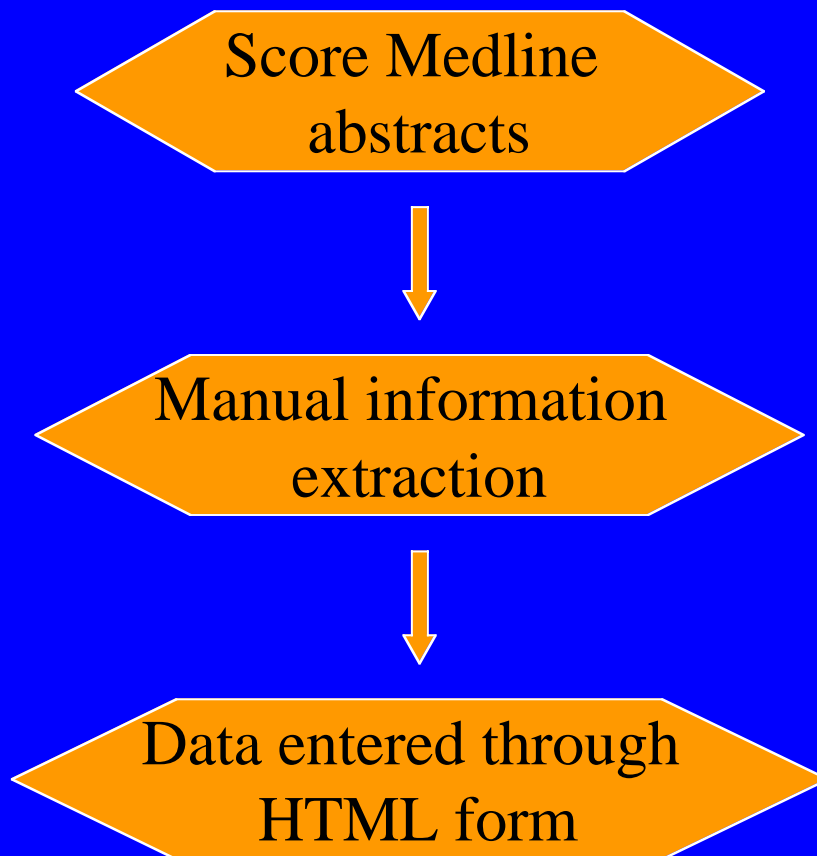
Articles	1,802
Proteins	6,810
Interactions	17,391
Live interactions	408

Reference: Marcotte EM et al. Bioinformatics. 2001 17(4):359-63

DIP and Universe of Biological Protein Interactions

Universe of Biological Protein Interactions

DIP

LiveDIP

How many are biologically relevant?

Outline

- Compile protein interaction database
- Assess the reliability of protein interactions
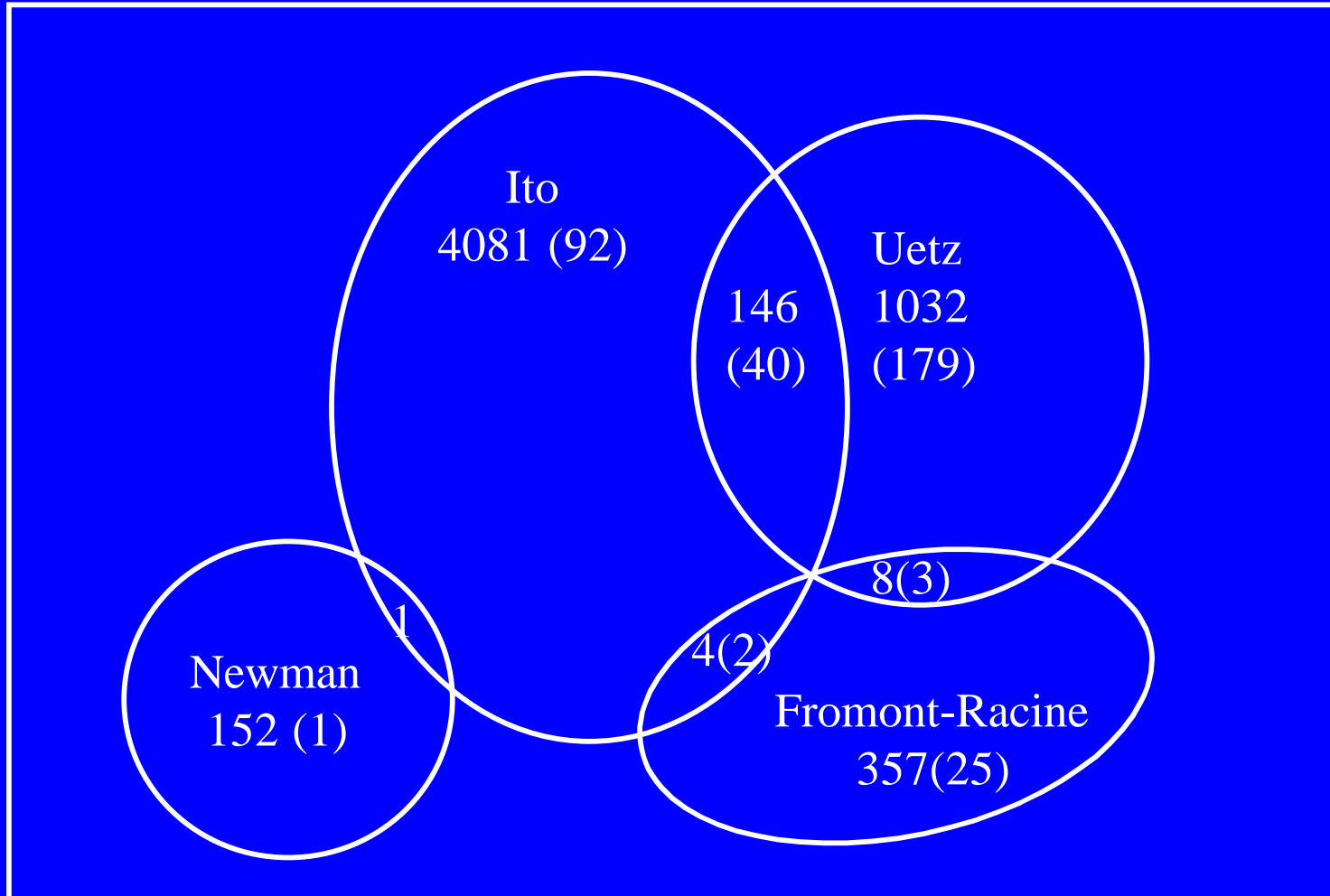- Analyze protein interaction networks

Protein Interactions in DIP

1

>3

3

2

Y2H
large

others

Y2H
small
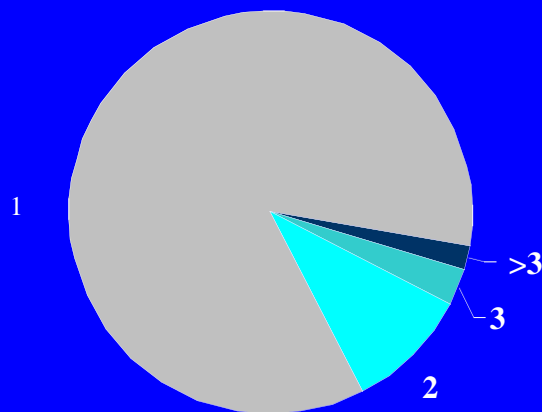
No. of experiments

Method of Detection

Large-scale Data Overlap Poorly

Ito
4081 (92)

Uetz
1032
(179)

146
(40)

8(3)

4(2)

1

Newman
152 (1)

Fromont-Racine
357(25)

Expression Profile Reliability Index (EPR Index) α_{EPR} Estimates Fraction of Correct Interactions

Interacting and non-interacting protein pairs show different distribution of their mRNA expression distance.

$$\rho_{exp} = \alpha \leftarrow \rho_i + (1-\alpha) \leftarrow \rho_{ni}$$

$\alpha_{EPR}=0.31$
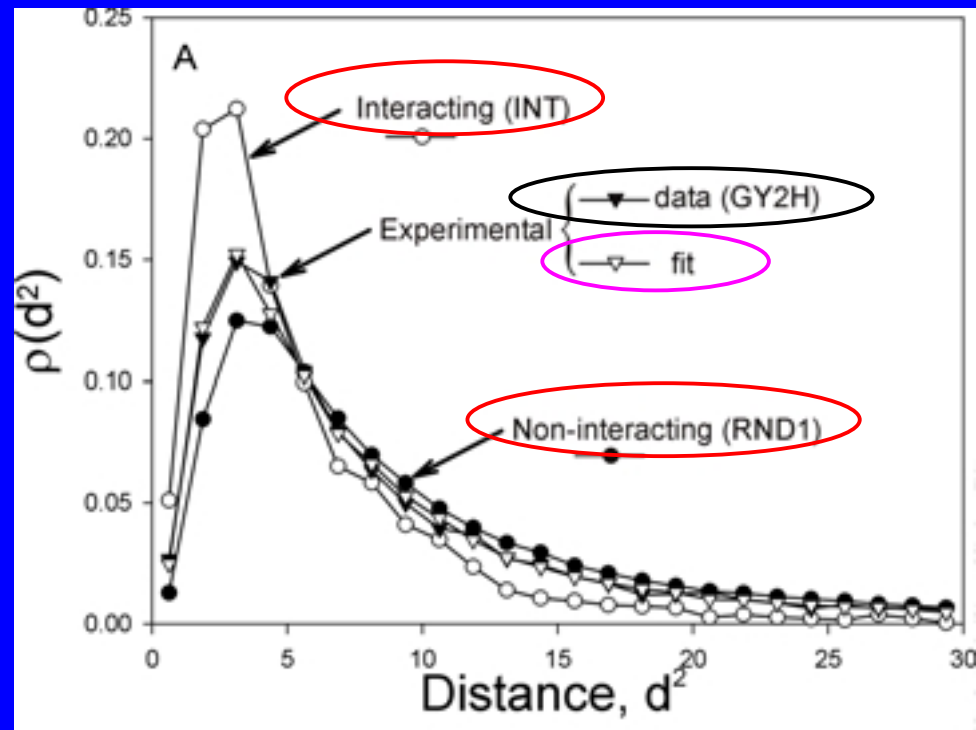
Expression Profile Reliability Index α_{EPR} Estimates Fraction of Correct Interactions

Dataset	Fraction of correct interactions α_{EPR}
Global yeast two-hybrid	0.31
DIP yeast interactions	0.48
Verified by 2 experiments	0.85
Verified by 3 experiments	0.88

EPR Index α_{EPR} Reflects the Overall Quality of Large-scale Datasets
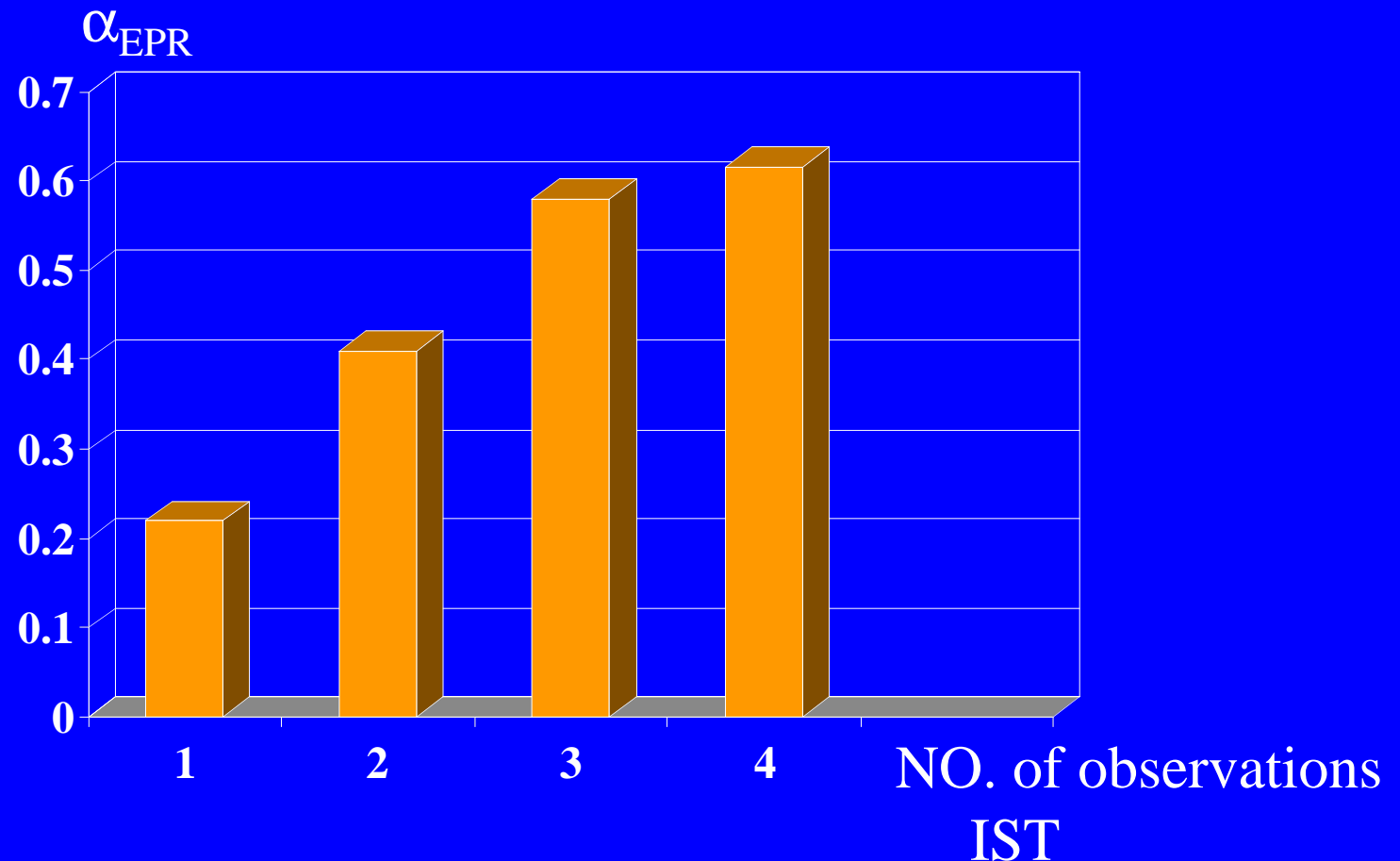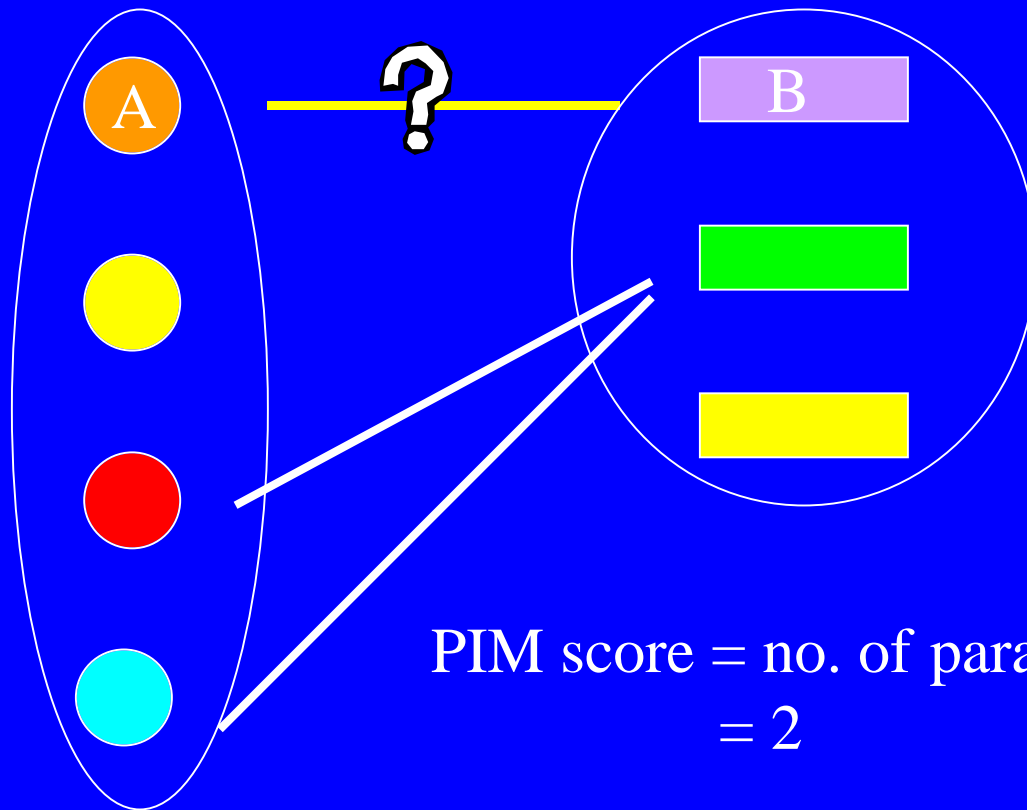
Reference: Ito T et al. Proc Natl Acad Sci U S A. 2001 98(8):4569-74.

Assess protein interactions

Paralogous Interaction Method (PIM)

A

B

PIM score = no. of paralogous interactions
= 2

Selectivity: ~ 99%
Sensitivity: ~ 50%
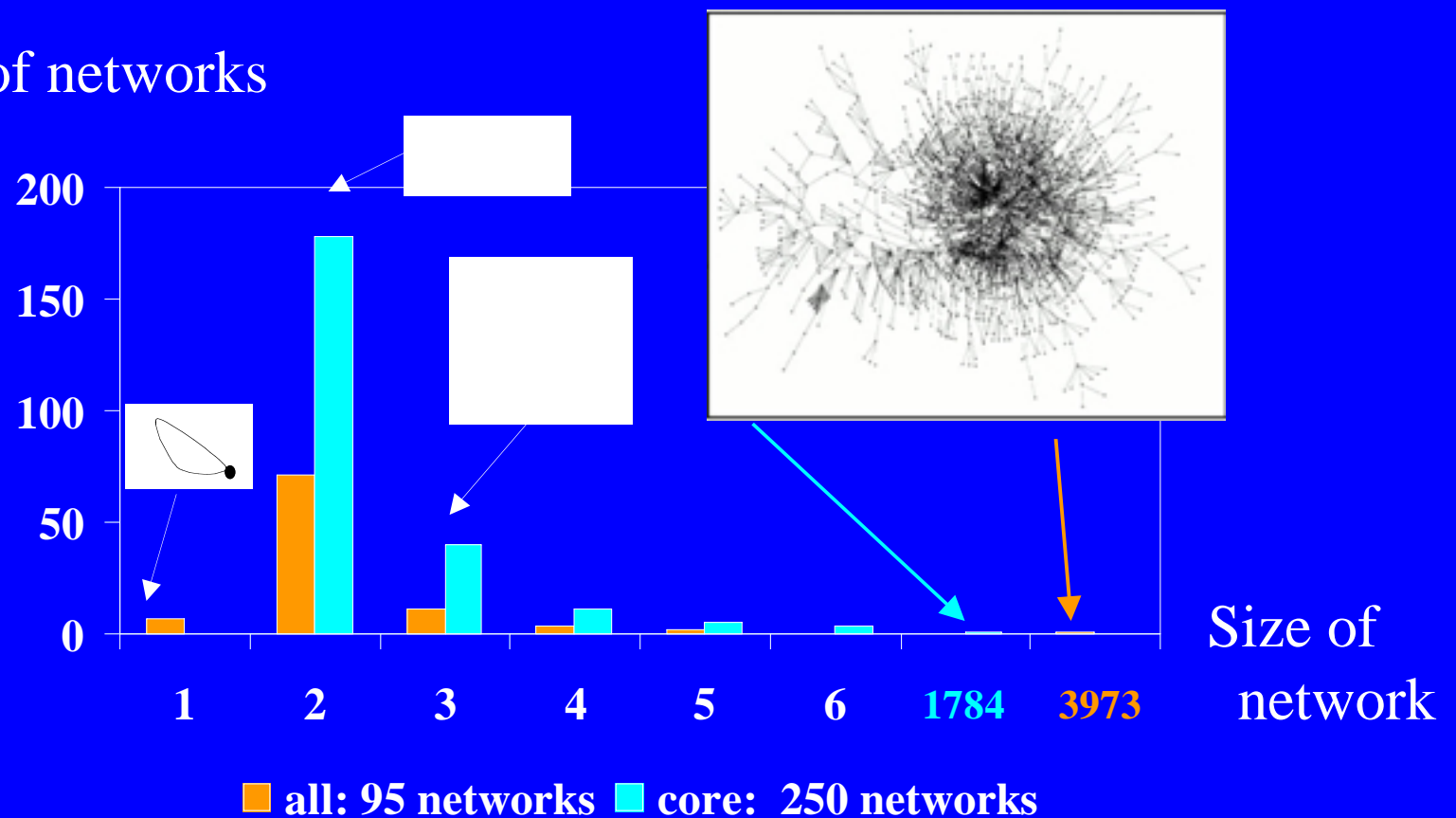
Dataset of Confident Protein Interactions
CORE

CORE

3003

Interactions in yeast

DIP
8063
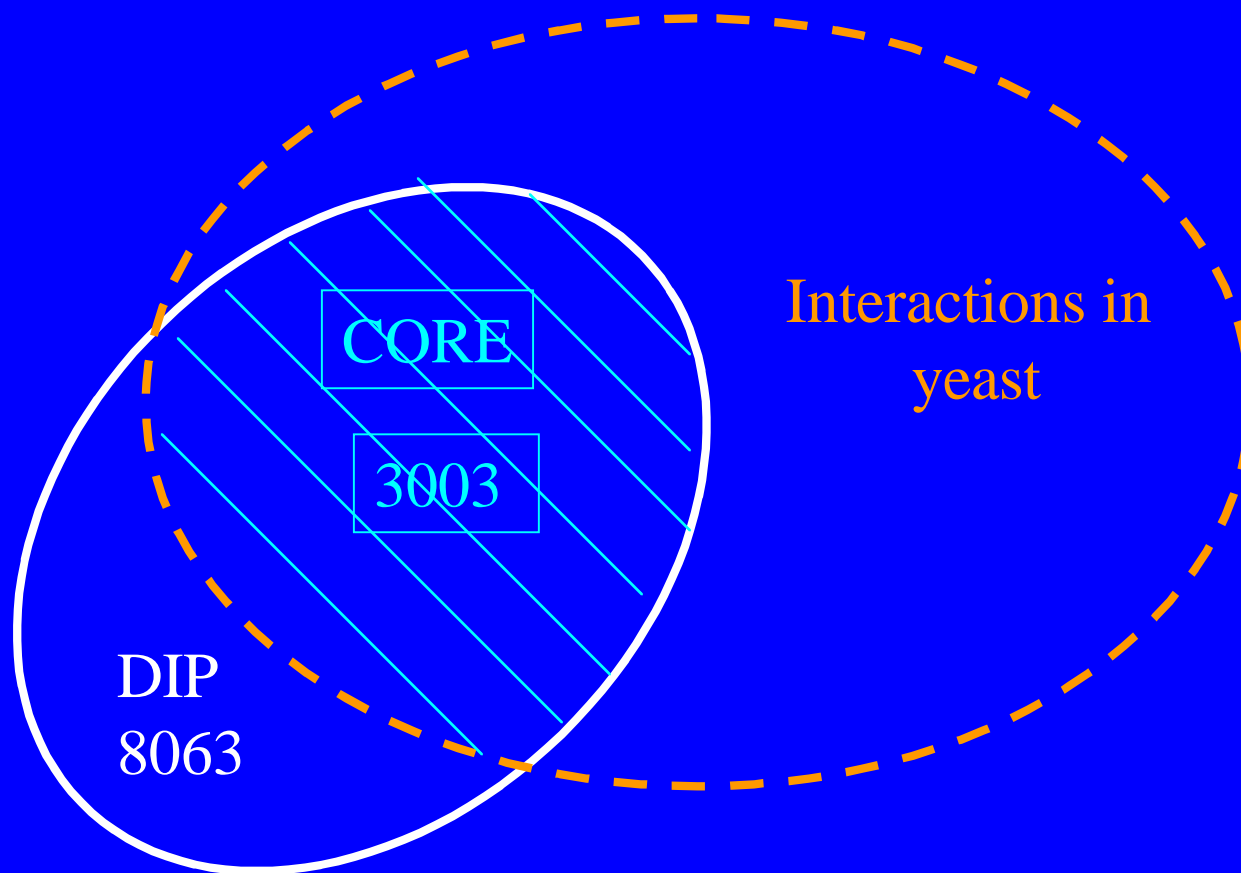
Outline

- Compile protein interaction database

- Assessing protein interactions computationally
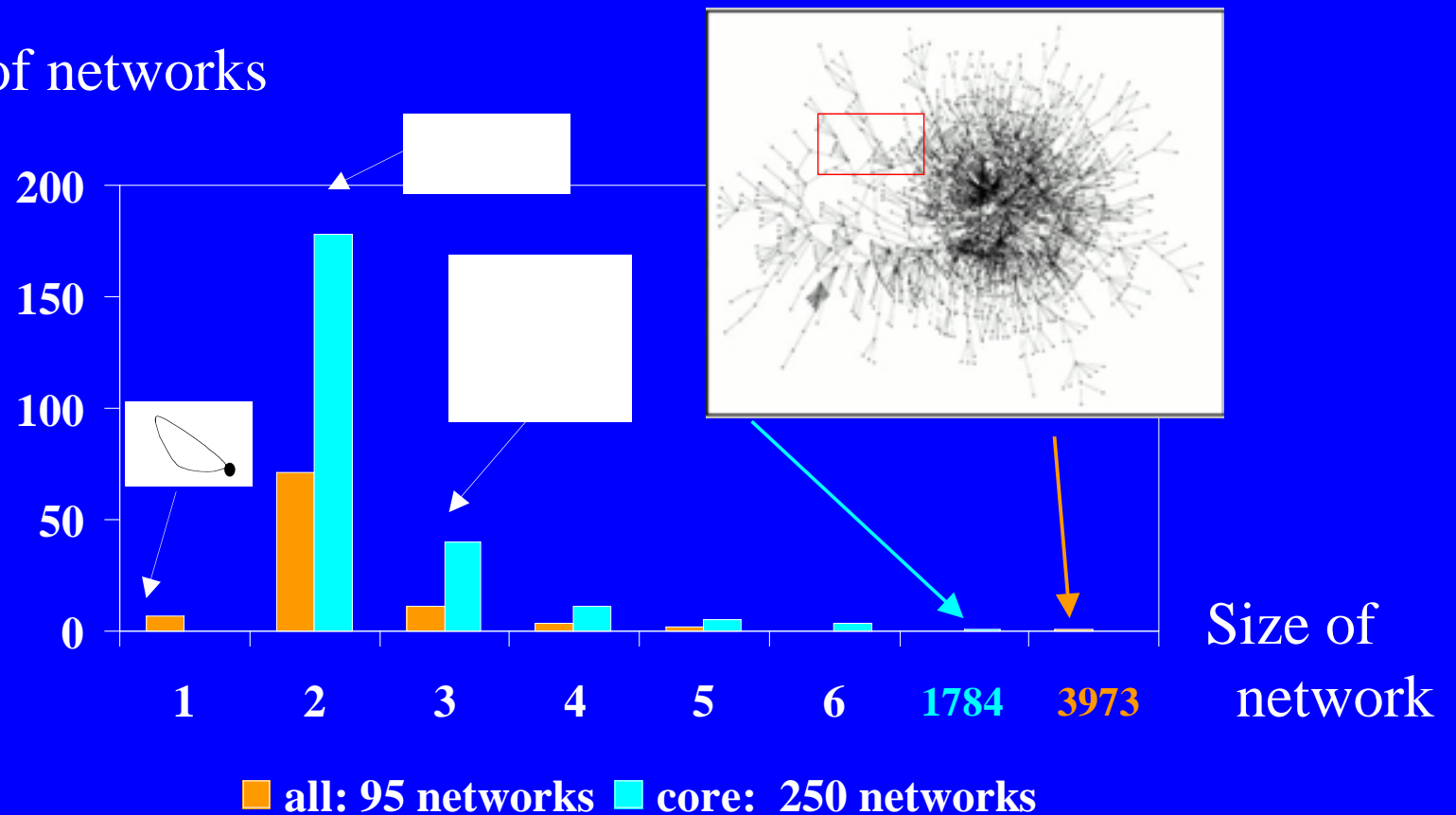
- Analyze protein interaction network

Interacting Proteins Form One Big Network and Several Small Ones
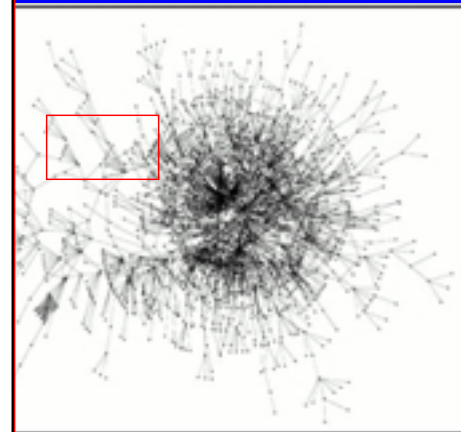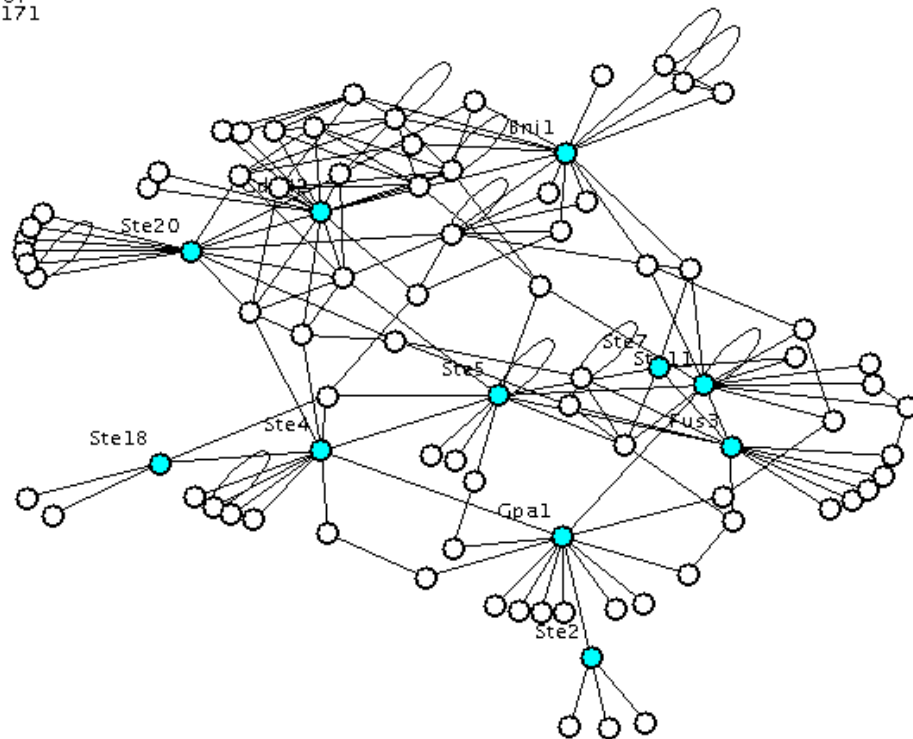
Number of networks

Size of network

1   2   3   4   5   6   1784   3973

■ all: 95 networks   ■ core: 250 networks

Interacting Proteins Form One Big Network and Several Small Ones

Number of networks

200

150

100

50

0

1   2   3   4   5   6   **1784**   **3973**

Size of network

■ **all: 95 networks**   ■ **core: 250 networks**

Interacting Proteins Form One Big Network and Several Small Ones

Nodes: 87
Edges: 171

Interaction network around pheromone signaling proteins

Size of network

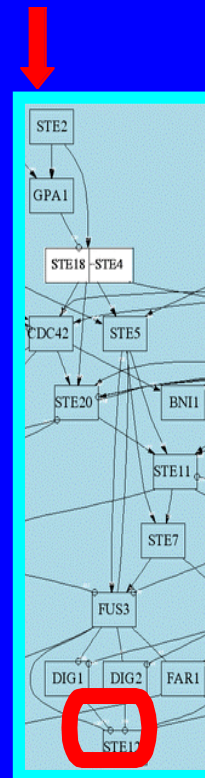6   1784   3973

■ all: 95 networks   ■ core: 250 networks

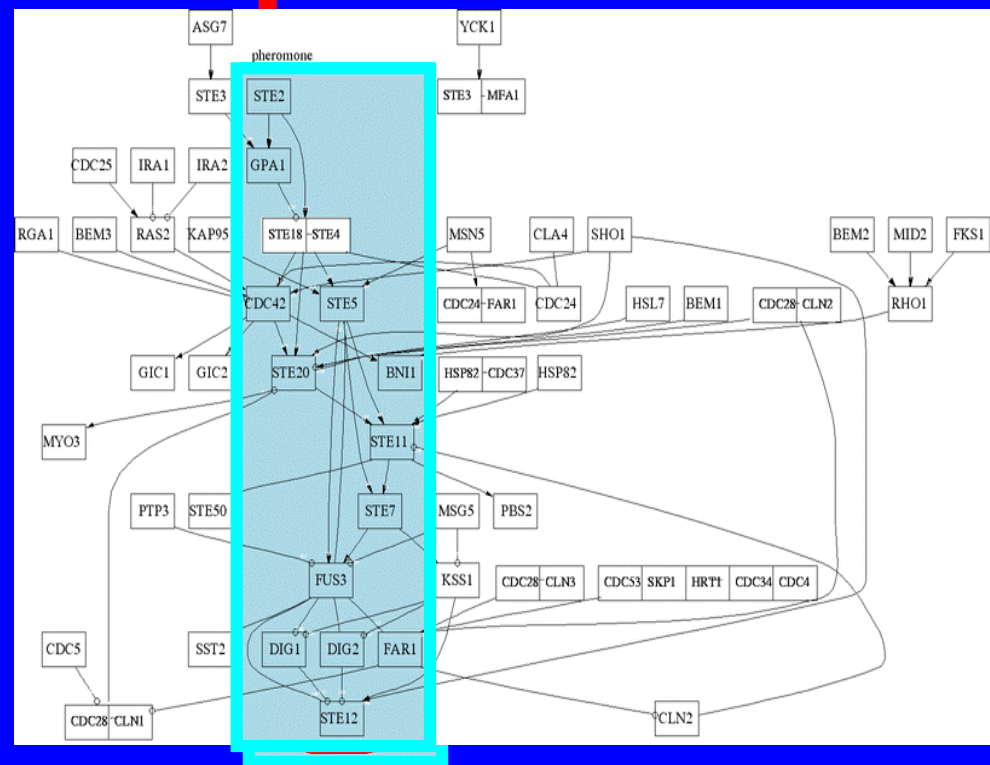# Analyze protein networks

Signaling Pathway

Signaling Pathway

Signaling Pathway

Signaling Pathway

Analyze protein networks

- Functions within the interaction network;

Signaling Pathway
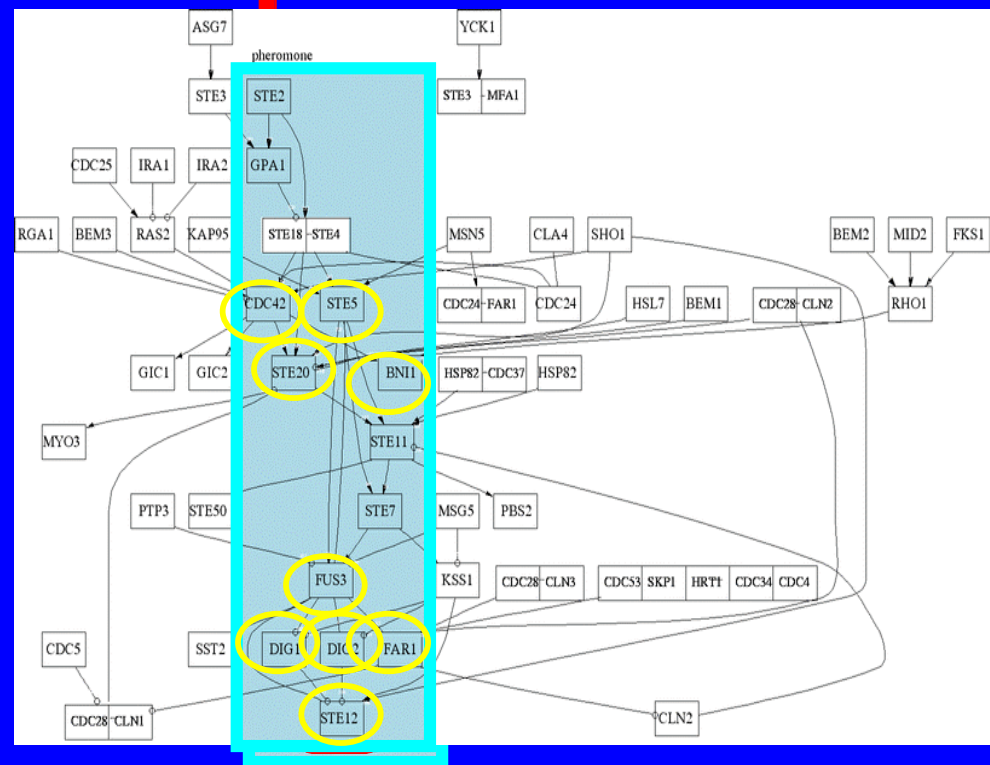
- Functions within the interaction network;

Signaling Pathway

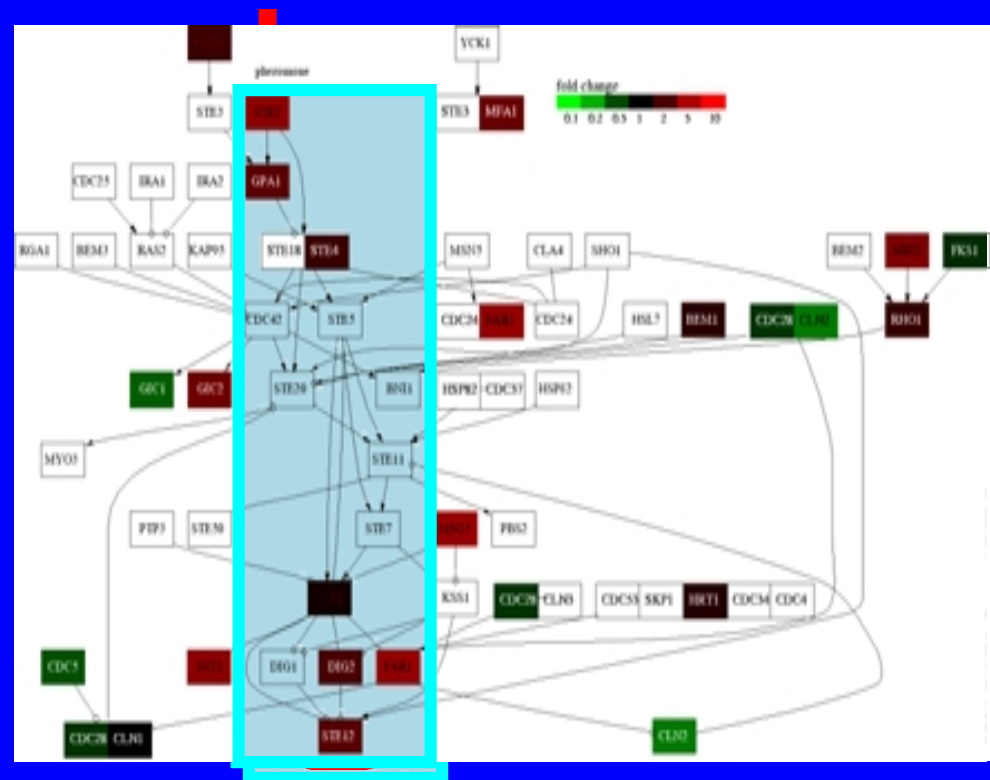- Functions within the interaction network;

- Modulated at many steps by both positive and negative regulations.

Signaling Pathway

- Functions within the interaction network;

- Modulated at many steps by both positive and negative regulations.

Signaling Pathway

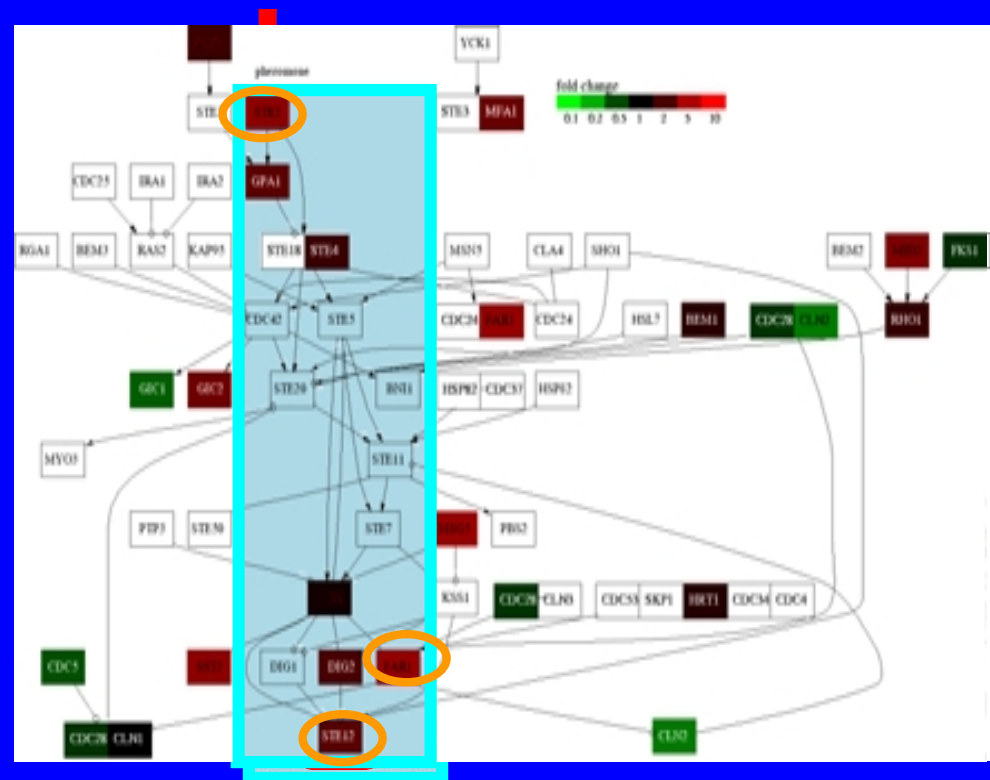- Functions within the interaction network;

- Modulated at many steps by both positive and negative regulations.

Signaling Pathway

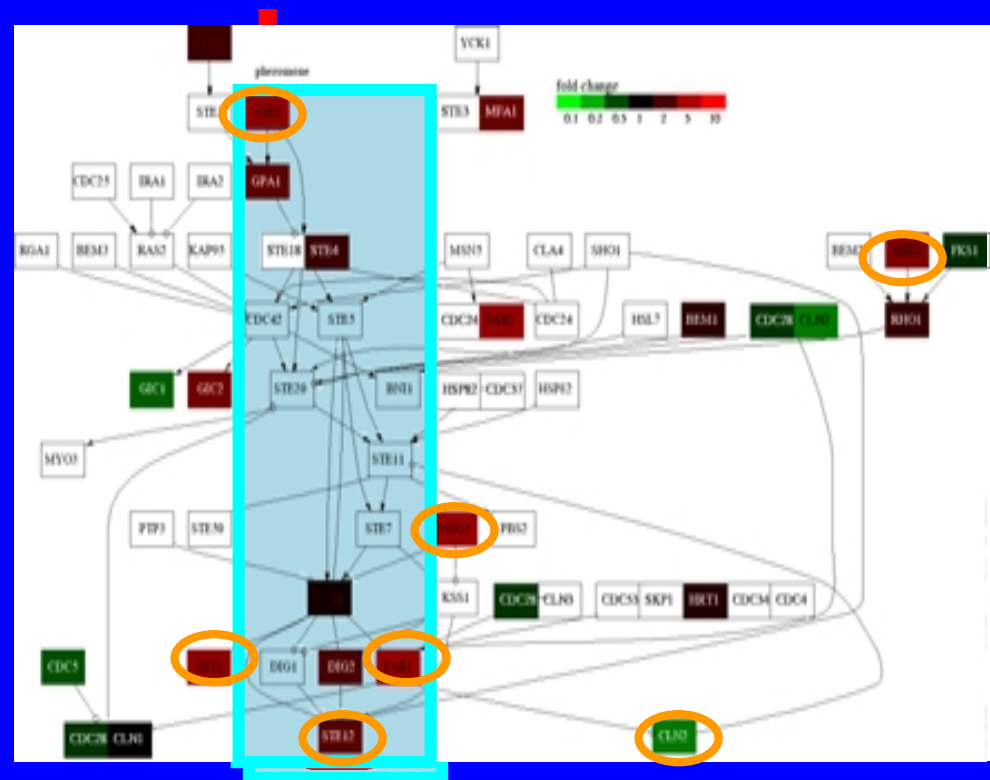- Functions within the interaction network;

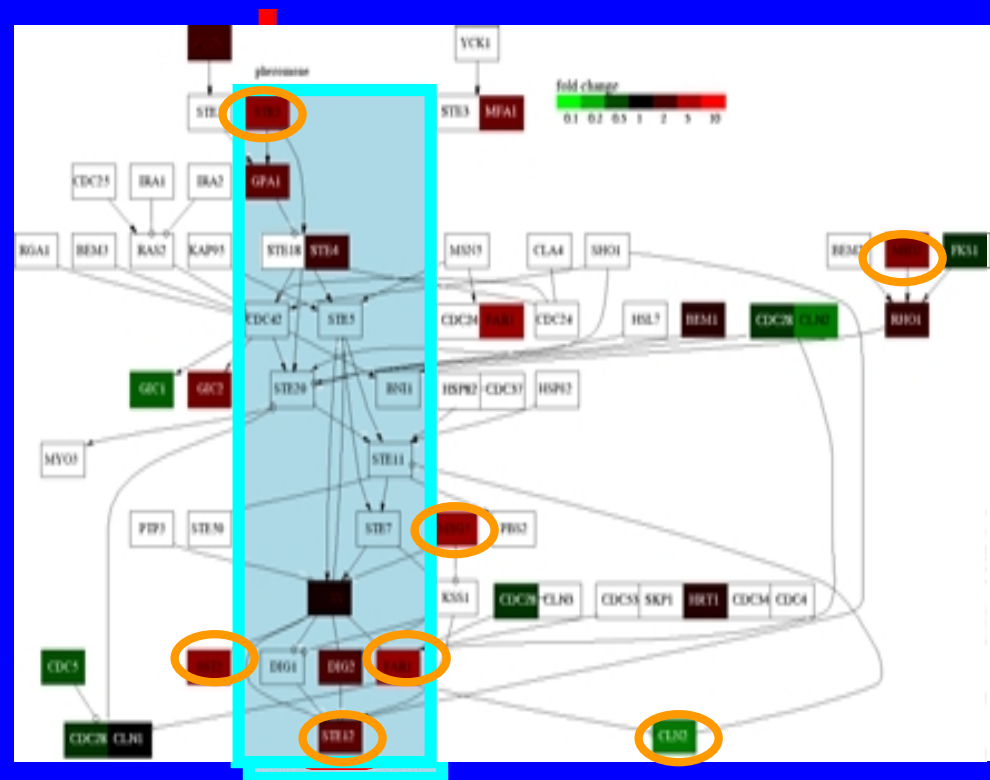- Modulated at many steps by both positive and negative regulations.

Signaling Pathway

- Functions within the interaction network;

- Modulated at many steps by both positive and negative regulations.

- Regulated through changes in the amount of proteins and changes in protein states.

Summary

- DIP allows access to protein interactions.

- Benchmark: PIM and EPR assess reliability of large scale interaction data.

- DIP data and tools provide insights into properties of protein interaction related biological processes.

- The above analysis will be extended to study the protein interaction networks of DOE-priority organisms.

References:

- Xenarios I, Salwinski L, Duan XJ, Higney P, Kim SM, and Eisenberg D. DIP, the Database of Interacting Proteins: a research tool for studying cellular networks of protein interactions. Nucleic Acids Res. 2002, 30(1): 303-5.

- Duan XJ, Xenarios I, and Eisenberg D.   Describing Biological Protein Interactions in Terms of Protein States and State Transitions: the LiveDIP Database. Manuscript accepted.

- Deane CM, Salwinski L, Xenarios I, and Eisenberg D. Protein Interactions: Two Methods for Assessment of the Reliability of High-throughput Observations. Manuscript submitted.

Related Work:

- Graeber TG, Eisenberg D. Bioinformatic identification of potential autocrine signaling loops in cancers from gene expression profiles. Nat Genet. 2001 Nov;29(3):295-300.

http://dip.doe-mbi.ucla.edu